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PHOTO-STIMULATED HETEROLYSIS OF THE C(=O)–O BOND IN (*Z*)-*N*-ACETYL-α-DEHYDROPHENYLALANINE ARYL ESTER DERIVATIVES

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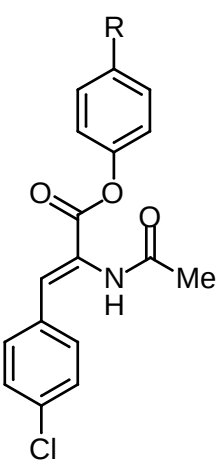
Abstract—The irradiation of the title compounds [(*Z*)-**1**] in acetonitrile was found to give (*Z*)-2-methyl-4-(4-chlorobenzylidene)-5(4*H*)-oxazolone [(*Z*)-**2**] and phenols or naphthols (**3**), along with minor amounts of the Fries-rearranged products (**4**) and (*E*)-**2**. Solvent and substituent effects on the product distribution confirmed that the heterolytic cleavage of the ester C(=O)–O bond of the starting **1** in the excited singlet state is responsible for appearance of both **2** and **3** whereas **4** is derived from the homolysis (of the ester bond) taking place in competition with the predominant heterolysis of this bond. It was suggested that there is a pronounced contribution of charge transfer from the aryloxy oxygen to the parent π system in the excited singlet state.

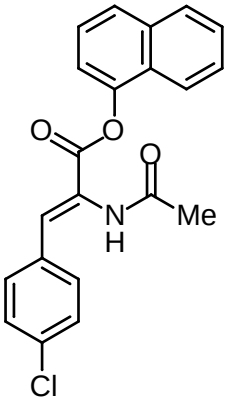
Photochemistry has continued to contribute to the development of efficient and selective transformations of organic materials into pharmaceutically important heterocyclic compounds.[1] In the course of our systematic study towards the characterization of the excited-state reactivities of *N*-acyl-α-dehydroamino acid derivatives, we have discovered some interesting photocyclization reactions in these dehydroamino acids.[2,3] One of the important findings is that the irradiation of substituted (*Z*)-*N*-acetyl-α-dehydrophenylalaninamides in acetonitrile give isoquinoline and 1-azetine derivatives in comparable yields[2a,c] while the selective formation of isoquinolines is observed when (*Z*)-*N*-acetyl-α-dehydrophenylalanine alkyl esters is irradiated under the same conditions.[2d] It was suggested that strong electronic repusion between lone pairs of electrons on the ring nitrogen and on the ethoxy oxygen in an azetidine intermediate is responsible for the exclusive deactivation of the excited-state (*E*)-isomer, the precursor of 1-azetine derivative. If we introduce an aryl group (instead of an alkyl) into *N*-acetyl-α-dehydrophenylalanine alkyl esters, it may be expected that a strong tendency of the lone pair of electrons on the aryloxy oxygen to be delocalized onto an aromatic ring in the excited singlet state exerts a large effect on the excited-state reactivities of both the (*Z*)- and (*E*)-isomers.[4]

Recently, photochemical control of homolytic *versus* heterolytic bond-cleavage pathway has been the subject of extensive research efforts[5–8] because of its potential application to developing protecting groups

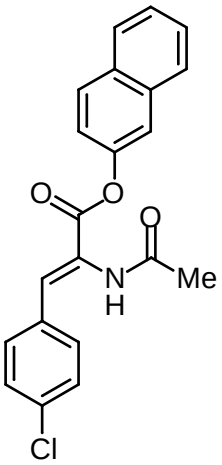
of biological molecules[5] as well as photoinitiators with high selectivities.[6] It is, thus, significant to investigate the relative contribution of the ester C(=O)–O bond cleavage process (heterolytic versus homolytic) and the photocyclization (eventually affording isoquinoline and 1-azetine derivatives) to the overall photochemical processes of (*Z*)-*N*-acetyl-α-dehydrophenylalanine aryl ester model compounds [(*Z*)-**1a**–**d**], which were designed and synthesized for this investigation. We now present results which demonstrate that the model aryl ester derivatives studied undergo predominant heterolytic cleavage of the C(=O)–O bond with a small or a negligible contribution of the homolysis of this bond and the cyclization of the (*Z*)- and (*E*)-isomers in their excited states.



(*Z*)-**1a** (R = H)
(*Z*)-**1b** (R = OMe)

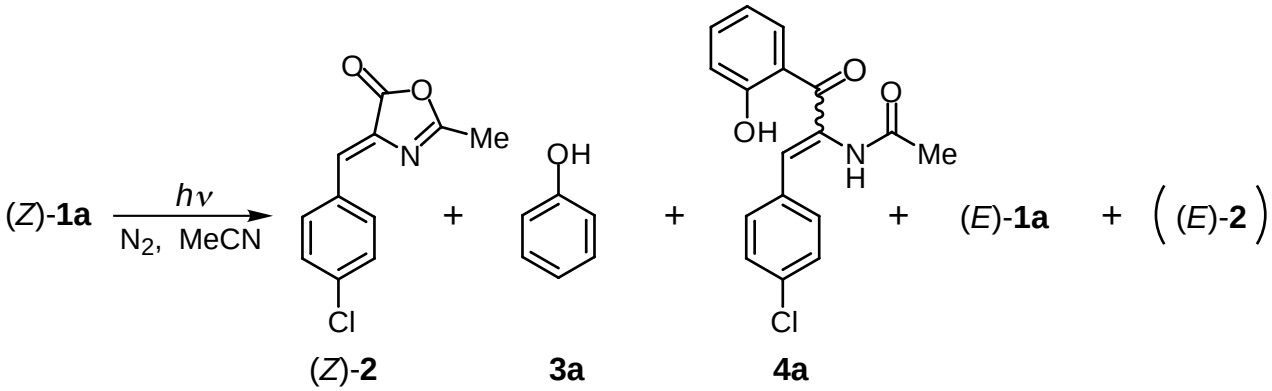


(*Z*)-**1c**



(*Z*)-**1d**

The starting (*Z*)-isomers were prepared by the ring-opening reactions of (*Z*)-2-methyl-4-(4-chlorobenzylidene)-5(4*H*)-oxazolone [(*Z*)-**2**] with phenols or naphthols in chloroform containing triethylamine.[9] After a nitrogen-purged acetonitrile solution of (*Z*)-**1a** (4.0×10^{-3} mol dm^{-3}, 500 mL) was irradiated with Pyrex-filtered light (>280 nm) from a 450 W high-pressure Hg lamp for 2 h at room temperature, the product mixture obtained was subjected to preparative thin-layer and/or column chromatography over silica gel, which allowed us to isolate (*Z*)-**1a** (23% yield), (*E*)-**1a** (26%), (*Z*)-**2** (19%), and phenol (**3a**, 23%) along with a small amount of the Fries-rearranged product (**4a**, 1%) (Scheme 1).[10] A careful ^{1}H NMR spectral analysis of the product mixture suggested the formation of a detectable amount of (*E*)-**2** whose methyl and aromatic proton signals were detected at 2.30 and 8.13 ppm,[3] though any attempts to isolate (*E*)-**2** of analytical grade were not fruitful.[11] In addition, we could not detect proton signals characteristic of isoquinoline and 1-azetine derivatives. Unfortunately, large overlapping of the methyl or aromatic proton signals of products made it impossible to trace the reaction and to estimate the composition of each compound quantitatively by means of ^{1}H NMR spectroscopy. According to the same procedure as above, we were able to isolate each product from the reaction mixture obtained by the 2 h irradiation of (*Z*)-**1b**–**d** in acetonitrile, as shown in Table 1. The composition of **2** and **3** has a tendency to increase when the naphthyl group is introduced instead of the phenyl, whereas the reverse is observed for the Fries-rearranged product (**4**).



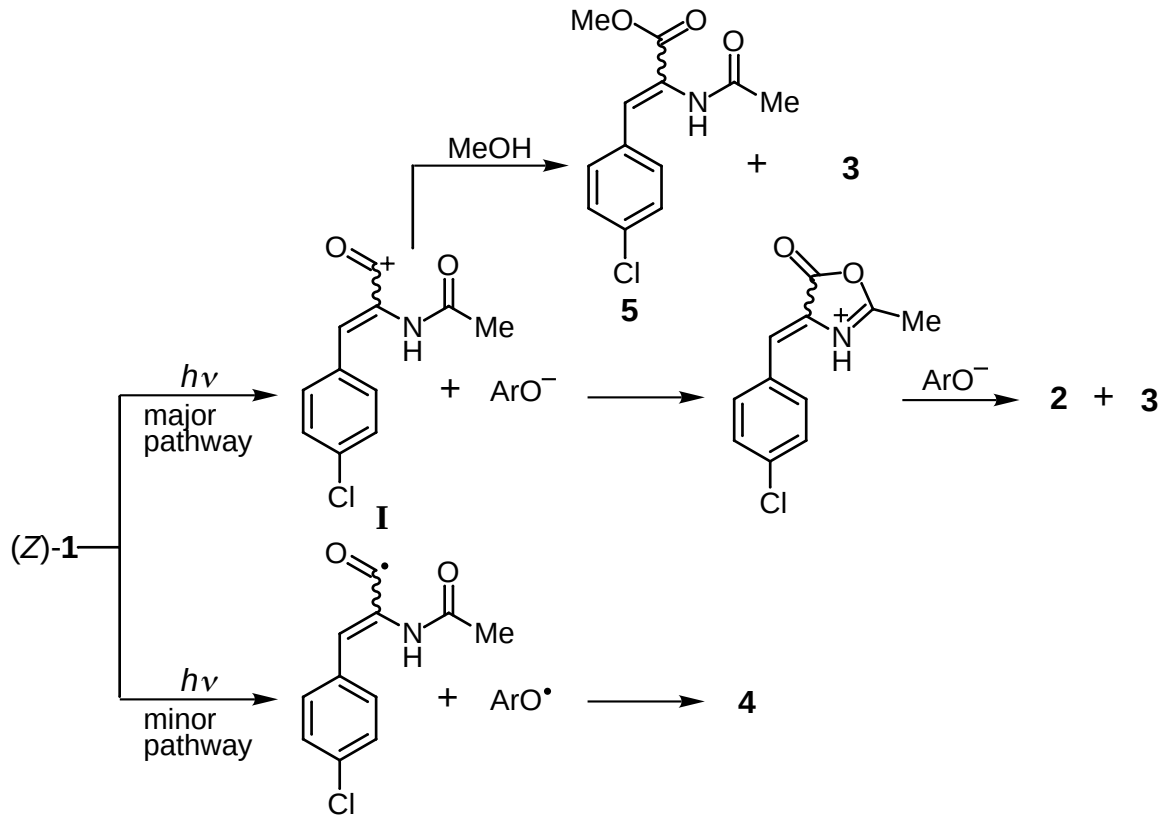
Scheme 1

Table 1. Isolated yields of each compound obtained by the 2 h irradiation of (*Z*)-**1a**–**d** in acetonitrile at room temperature

Compound	Yields (%)				
	(*Z*)-**1**	(*E*)-**1**	(*Z*)-**2**	**3**	**4**
(*Z*)-**1a**	23	26	19	23	1
(*Z*)-**1b**	34	30	20	14	1
(*Z*)-**1c**	26	25	23	21	<1
(*Z*)-**1d**	35	27	24	20	–[a]

a) Not detected.

The fact that the photo-Fries rearrangements[12] as well as acyloxy photomigrations[13] proceed mainly through a caged singlet radical pair intermediate suggests the involvement of the homolytic C(=O)–O bond cleavage that is responsible for the appearance of **4a**. On the other hand, the assumption that the heterolytic cleavage of the ester C(=O)–O bond occurs in competition with the homolysis of this bond in the excited state forces us to predict that an acylium ion intermediate (**I**) generated should be captured by methanol to afford the corresponding methyl ester derivative. The 2 h irradiation of (*Z*)-**1c** (4.0×10^{-3} mol dm^{-3}) in methanol, chosen as the starting dehydrophenylalanine aryl ester derivative, allowed us to isolate the methyl ester (**5**) as a mixture of the (*Z*)- and (*E*)-isomers in 15% yield in addition to (*Z*)-**1c**, (*E*)-**1c**, (*Z*)-**2**, and 1-naphthol (**3c**), being consistent with our prediction.[14] Thus, we are led to propose Scheme 2 that provides a good explanation for the product distribution derived from the photolysis of **1** in acetonitrile and also in methanol. As already described, the irradiation of (*Z*)-**1a** in acetonitrile gave a slight amount of (*E*)-**2** despite the remarkable formation of (*E*)-**1a**. Because (*Z*)-**1a** is thermodynamically more stable than the corresponding (*E*)-isomer, it is possible that the intermediate (**I**) derived from the latter isomer mostly

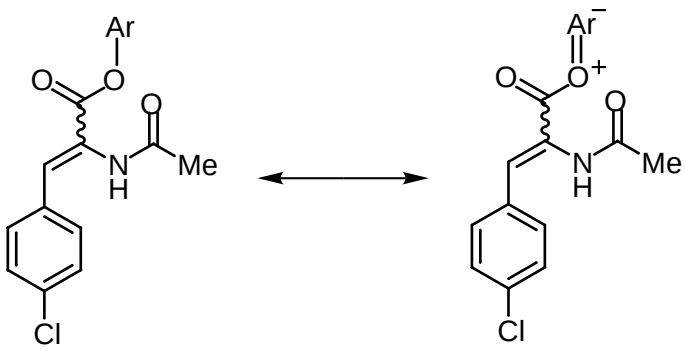


Scheme 2

cyclized into the (*Z*)-oxazolone derivative. This possibility is substantiated by the observation that on irradiation of (*E*)-**1a** (4.0×10^{-3} mol dm^{-3}) in acetonitrile for 2 h, (*Z*)-**2** is obtained as one of the major products, along with minor amounts of (*E*)-**2** and **4a** (^{1}H NMR spectral analysis).

Since there remains a possibility that the dissociation reaction of (*Z*)-**1** proceeds also in the ground state eventually giving (*Z*)-**2** and **3**, an acetonitrile-d_3 solution of (*Z*)-**1a**, placed in an NMR tube, was allowed to stand for 24 h at room temperature. A ^{1}H NMR spectral analysis of the solution showed that there appeared detectable amounts of (*Z*)-**2** and **3a**. Interestingly, the introduction of the strong electron-withdrawing CF_3 group at the 4-position of the phenoxy moiety [(*Z*)-**1e**, R= CF_3] greatly accelerated the ground-state reaction in acetonitrile-d_3 to afford (*Z*)-**2** and 4-trifluoromethylphenol in a nearly 1:1 stoichiometric ratio (about half the starting **1e** was converted to these two products in a few hours). These observations demonstrate that **2** and **3a**–**d** are produced predominantly through heterolytic cleavage of the ester C(=O)–O bond in **1a**–**d** and, hence, provide definitive evidence for a mechanism shown in Scheme 2.

It is well-known that the proton dissociation ability of phenol and naphthol is dramatically enhanced in the excited singlet state, because charge transfer from the hydroxy oxygen to the parent π system takes place to a much larger degree in the excited state than in the ground state as already described.[4] Thus, the finding that the ester C(=O)–O bond in **1a**–**d** has a marked tendency to undergo heterolytic cleavage in the excited state indicates a pronounced contribution of the resonance structure (**II**), and also substantiates a mechanism in which the heterolysis of the ester bond (giving **2** and **3**) occurs in competition with the homolysis of this bond (yielding **4**) from the excited singlet state (Scheme 2).



II

ACKNOWLEDGMENT

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10. Selected data for (*Z*)-**1a**: mp 175.0–176.0 ℃ ($CHCl_3$-hexane); IR (KBr) ν/cm^{-1}= 3214, 1728, 1659,

1248; ^{1}H NMR (500 MHz, DMSO-d_6) δ= 2.06 (3H, s), 7.16 (2H, d, J= 7.3 Hz), 7.29 (1H, dd, J= 7.3, 7.3 Hz), 7.31 (1H, s), 7.45 (2H, dd, J= 7.3, 7.3 Hz), 7.52 (2H, d, J= 8.6 Hz), 7.73 (2H, d, J= 8.6 Hz), 9.92 (1H, s); ^{13}C NMR (DMSO-d_6) δ= 22.3, 121.5 (2C), 125.8, 128.6 (2C), 129.4 (2C), 129.9, 130.0, 131.5 (2C), 132.1, 133.9, 150.7, 163.9, 169.7. Anal. Calcd for $C_{17}H_{14}NO_3Cl$: C, 64.67; H, 4.47; N, 4.44. Found: C, 64.65; H, 4.52; N, 4.46.

For (*E*)-**1a**: mp 142.0–143.0 ℃ ($CHCl_3$-hexane); IR (KBr) ν/cm^{-1}= 3334, 1740, 1680, 1269; ^{1}H NMR (500 MHz, DMSO-d_6) δ= 2.03 (3H, s), 6.62 (1H, s), 7.08 (2H, d, J= 7.9 Hz), 7.26 (1H, dd, J= 7.3, 7.3 Hz), 7.36 (2H, d, J= 8.5 Hz), 7.43 (2H, dd, J= 7.3, 7.9 Hz), 7.46 (2H, d, J= 8.5 Hz), 10.37 (1H, s); ^{13}C NMR (DMSO-d_6) δ= 22.1, 118.6, 121.2 (2C), 125.9, 128.4 (2C), 129.3, 129.4 (2C), 129.8 (2C), 132.3, 132.8, 150.2, 163.0, 168.6. Anal. Calcd for $C_{17}H_{14}NO_3Cl$: C, 64.67; H, 4.47; N, 4.44. Found: C, 64.63; H, 4.61; N, 4.29.

For (*Z*)-**2**: mp 143.0–144.0 ℃ ($CHCl_3$-hexane); IR (KBr) ν/cm^{-1}= 1800, 1773, 1659, 1260; ^{1}H NMR (500 MHz, DMSO-d_6) δ= 2.40 (3H, s), 7.24 (1H, s), 7.58 (2H, d, J= 8.5 Hz), 8.20 (2H, d, J= 8.5 Hz); ^{13}C NMR (DMSO-d_6) δ= 15.3, 128.1, 128.9 (2C), 131.9, 133.0, 133.4 (2C), 135.6, 167.1 (2C). Anal. Calcd for $C_{11}H_8NO_2Cl$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.27; H, 3.77; N, 6.02.

For **3a**: mp 39.0–41.0 ℃ (EtOAc-hexane); ν/cm^{-1}= 3316, 3040; ^{1}H NMR (500 MHz, DMSO-d_6) δ= 6.75 (2H, d, J= 8.6 Hz), 6.77–7.67 (1H, m), 7.15 (2H, dd, J= 7.3, 8.6 Hz), 9.31 (1H, s); ^{13}C NMR (DMSO-d_6) δ= 115.2 (2C), 118.7, 129.3 (2C), 157.3. These physical and spectroscopic data were consistent with those of commercially available authentic sample.

For **4a**: oily liquid; ^{1}H NMR (500 MHz, DMSO-d_6) δ= 1.93 (3H, s), 6.62 (1H, s), 6.78 (1H, dd, J= 7.3, 7.9 Hz), 6.91 (1H, d, J= 7.9 Hz), 7.09 (2H, d, J= 8.5 Hz), 7.22 (2H, d, J= 8.5 Hz), 7.42 (1H, ddd, J= 1.8, 7.3, 7.9 Hz), 7.57 (1H, dd, J= 1.8, 7.9 Hz), 10.38 (1H, s), 11.32 (1H, s); ^{13}C NMR (DMSO-d_6) δ= 22.0, 115.4, 117.4, 119.1, 120.4, 128.3 (2C), 129.7 (2C), 131.2, 131.7, 133.1, 134.7, 135.9, 160.5, 167.8, 197.0. The low isolated yield of **4a** made it impossible to determine its physical properties. The fact that the δ value of the *N*-acetyl amide proton signal (10.38 ppm) of **4a** is equal to that of (*E*)-**1a** (10.37 ppm) strongly suggests the (*E*)-configuration of the Fries-rearranged product obtained.

11. Selected data for (*E*)-**2**: yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ= 2.30 (3H, s), 7.55 (1H, s), 7.56 (2H, d, J= 8.6 Hz), 8.13 (2H, d, J= 8.6 Hz). We succeeded in isolating a slight amount of (*E*)-**2** whose ^{1}H NMR spectrum was consistent with the proposed structure, although this *E*-isomer was contaminated with (*E*)-**1a** and **3a**.
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14. Selected data for (*Z*)-**5**: mp 155.0–156.0 ℃ (EtOAc-hexane); IR (KBr): ν/cm^{-1}= 3214, 1734, 1668, 1248; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 2.00 (3H, s), 3.71 (3H, s), 7.16 (1H, s), 7.48 (2H, d, J=

8.5 Hz), 7.64 (2H, d, *J*= 8.5 Hz), 9.65 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ= 22.4, 52.2, 127.2, 128.6 (2C), 129.6, 131.4 (2C), 132.3, 133.7, 165.4, 169.4. Anal. Calcd for $C_{12}H_{12}NO_3Cl$: C, 56.82; H, 4.77; N, 5.52. Found: C, 56.82; H, 4.65; N, 5.38.

For (*E*)-**5**: mp 99.0–100.0 ℃ (EtOAc-hexane); IR (KBr): ν/cm^{-1}= 3250, 1731, 1662, 1245 cm^{-1}; ^{1}H NMR (500 MHz,DMSO-d_6): δ= 1.96 (3H, s), 3.61 (3H, s), 6.50 (1H, s), 7.20 (2H, d, *J*= 8.6 Hz), 7.38 (2H, d, *J*= 8.6 Hz), 10.10 (1H, s); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ= 22.3, 51.8, 117.4, 128.3 (2C), 129.4 (2C), 129.7, 131.9, 133.1, 165.0, 168.1. Anal. Calcd for $C_{12}H_{12}NO_3Cl$: C, 56.82; H, 4.77; N, 5.52. Found: C, 56.76; H, 4.99; N, 5.21.